



# Haemophilia B PMS1 Gene SNPs Predictions through *In-silico* Approach at Proteomics Levels

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### Abstract

Hemophilia is one of the important hereditary disease that leading to deficiency in some clotting factors due to gene mutations beside this it related most important hematologic parts; anemia, the aim of this study is to identify the PMS1 (hemophilia B) gene SNPs and to predict mutation effects of this gene at the proteomic level, through in silico tools such as proven, sift, polyphen-2, I mutant suite-3, SNPs & GO, finally Meta-snp prediction. A according to these predictions tools & their confirmations I found that PMS1 gene SNPs showed damaging prediction which was considered as clinical manifestation in this study beside these a lots of SNPs illustrate decreasing in protein functionality; unfortunately 26 SNPs showed prediction results just with sift & proven predictions software and these explain why they were excluded from this study with those showed benign predictions by polyphen-2, in addition to confirmation of ORMDL1 gene SNPs that located at the same PMS1 gene chromosome had the same clinical effect such as PMS1 gene SNPs.

### Keywords

Haemophilia B; Clotting factors; Meta-snp prediction

### Introduction

Hemophilia B is characterized by deficiency in factor IX clotting activity due to mutation in factor IX gene, that results in prolonged oozing after injuries, tooth extractions, or surgery, and delayed or recurrent bleeding prior to complete wound healing. Hemophilia B is phenotypically indistinguishable from hemophilia A, it was first recognized as a different kind of hemophilia in 1952 with additional name Christmas disease; named after Stephen Christmas, the first patient who described with this disease. According to the level of factor IX clotting activity beside age of patients and frequency of bleeding episodes hemophilia are divided to 3 levels; mild, moderate and severe [1,2].

Individuals with mild hemophilia B do not have spontaneous bleeding and they often diagnosed later in their life with bleeding tendency once a year or once every ten years; however, without pre- and post-operative treatment, abnormal bleeding can happens

with surgery or tooth extractions, while in moderate hemophilia B they have spontaneous bleeding with prolonged or delayed oozing after relatively minor trauma and are usually diagnosed before age five to six years; the frequency of bleeding episodes varies from once a month to once a year, but in severe hemophilia B, spontaneous joint or deep-muscle bleeding is the most frequent symptom, those individuals are usually diagnosed during the first two years of life; without prophylactic treatment, they may average up to two to five spontaneous bleeding episodes each month [1].

Genetically; factor IX gene is located on the X chromosome (Xq27.1-q27.2), it's an X-linked recessive trait, which explain why only males usually affected. In addition in 1990, George Brownlee and Merlin Crossley showed that two sets of genetic mutations were preventing two key proteins from attaching to the DNA of people with a rare and unusual form of haemophilia B and haemophilia B Leyden, those people are suffering from excessive bleeding in childhood but it became rare after puberty, This deficiency lead to turning off the gene that produces clotting factor IX, which prevents excessive bleeding [2,3].

In this study I used different computational methods to identify the PMS1 (hemophilia B) gene SNPs and to predict mutation effects at the proteomic level.

### Materials and Methods

#### Hemophilia B retrieved sequence

Hemophilia B sequence was retrieved from NCBI through SNP search (<https://www.ncbi.nlm.nih.gov/snp/?term=haemeophilia%20B>); rs1145234 [*Homo sapiens*] in chromosome two (Chromosome: 2:189867833) for PMS1 gene, it is intron variant, missense, NC transcript variant Allele Origin: G (germline)/T (germline)/C (germline), this was selected from total SNPs 2347417 results.

#### Proven

Proven protein batch for human (PROVEAN v1.1.3.) (<http://provean.jcvi.org/index.php>) was selected in this study; PROVEAN is abbreviation for Protein Variation Effect Analyzer, its useful software for filtering sequence variants to identify nonsynonymous or indel variants that are predicted to be functionally important [4-6].

#### Sift Prediction (SIFT - Predict effects of nonsynonymous / missense variants)

(<http://sift.bii.a-star.edu.sg/>) SIFT dbSNP 138 was selected from batch tools from SIFT Sorting Intolerant From Tolerant software to predict whether an amino acid substitution affects protein function based on sequence homology and the physical properties of amino acids.

#### PolyPhen-2 (Polymorphism phenotyping v2)

PolyPhen-2 prediction of functional effects of human nsSNPs (<http://genetics.bwh.harvard.edu/pph2/index.shtml>) was used to predict the impact of an amino acid substitution on the structure and function of a human protein using straightforward physical and comparative considerations [7-10].

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## I-Mutant suite

I mutant.3 (<http://gpcr2.biocomp.unibo.it/cgi/predictors/I-Mutant3.0/I-Mutant3.0.cgi>) was used to predict protein stability changes upon single point mutation from: Protein Structure / Protein Sequence and also prediction of disease associated with single point mutation from Protein Sequence [11-13].

## SNPs and GO

SNPs & GO (<http://snps.biofold.org/snps-and-go/snps-and-go.html>) was used to predicting a disease associated variations by GO terms through SVM-based classifier, which takes in input protein sequence, profile and functional information to give output as disease-related or neutral with RI & scores [14-19].

**Meta-SNP** (Meta-predictor of disease causing variants) (<http://snps.biofold.org/meta-snp/#>) was used to confirm the results of previous methods; PANTHER, PhD-SNP, SIFT and SNAP, through the non-synonymous SNVs (nsSNVs), that's results in a single amino acid substitutions and may affect protein functions that lead to causing a disease [20-22].

## Results

### Proven

The total of 143 nsSNPs which was predicted by Proven prediction tools showed 83 snSNPs which are deleterious with in these 81 nsSNPs were damaging and 3 nsSNPs were tolerated according to sift prediction while 45 nsSNPs showed neutral prediction by proven with 33nsSNPs were damaging and 12 were tolerated according to Sift prediction but 15 snSNPs they were considered benign by polyphen-2 which were excluded from this study, please see details below with [Table 1](#).

In rs1145232; proven prediction showed 5 nsSNPs were deleterious with sift prediction damaging for all.

In rs5742973, according to proven prediction, 1 nsSNPs showed deleterious with sift prediction damaging.

In rs56309301; 1 nsSNPs showed neutral prediction by proven while sift prediction showed tolerated.

In rs61756360; according to proven prediction, 1 nsSNPs showed deleterious with sift prediction showed damaging, in rs111254723; 4 nsSNPs showed deleterious according to proven with sift prediction tolerated for all of them, in rs142159998; 3 nsSNPs showed deleterious by proven while sift prediction showed damaging for all, in rs143010673; according to proven prediction, 3 nsSNPs showed deleterious with sift prediction damaging for all, in rs143554211; 6 nsSNPs showed neutrals according to proven prediction with sift prediction showed damaging for all, in rs143686298; proven prediction showed 2 nsSNPs with neutrals prediction and damaging prediction by sift for all, in rs145103030; 5 nsSNPs showed deleterious according to proven prediction and damaging by sift prediction, in rs145521752; 6 nsSNPs where deleterious by proven prediction while sift prediction showed damaging for all, in rs147901996; 3 nsSNPs they were deleterious by proven with damaging sift prediction.

In rs148745528; 5 nsSNPs showed deleterious prediction by proven with damaging sift prediction predicts, in rs185306467; 3 nsSNPs showed deleterious prediction by proven with sift prediction damaging for the three, in rs188947672; 4 nsSNPs showed neutrals proven prediction and sift prediction damaging for all, in rs189785572; proven prediction showed 2 nsSNPs with neutral prediction and

damaging sift prediction for both, in rs193252599; proven predictions showed 2 nsSNPs predict neutral with sift prediction tolerated and damaging for each one of them, in rs199892342; proven prediction showed 1 nsSNPs with neutral prediction while sift prediction showed damaging predict, in rs200172149; according to proven prediction 1 nsSNPs showed neutral predict with tolerated sift prediction.

In rs200244068; proven prediction showed 2 nsSNPs deleterious in addition to damaging sift prediction for both, in rs200395679; proven prediction showed 1 nsSNPs showed neutral with damaging sift prediction, in rs200919195; according to proven prediction 1 nsSNPs showed neutral prediction with tolerated sift prediction, in rs201944922; 1 nsSNPs showed deleterious according to proven prediction while sift prediction showed damaging effect, in rs368282144; 5 nsSNPs showed deleterious proven prediction while sift prediction showed 3 nsSNPs with damaging and 2 nsSNPs they were tolerated.

rs369226504; according to proven prediction, 3 nsSNPs showed deleterious with 3 nsSNPs neutral while for sift prediction all of them showed damaging, in rs369814333; in proven prediction, 1 nsSNPs showed deleterious and the second one showed neutral with tolerated sift prediction for both, rs369909997; by proven prediction showed 1 nsSNPs neutral and tolerated sift prediction, rs370084230; 1 nsSNPs showed deleterious by proven prediction and damaging sift prediction, in rs370300640; According to proven prediction, 1 nsSNPs showed deleterious with sift prediction damaging, in rs370578519; 4 nsSNPs showed deleterious by proven prediction with damaging sift prediction for all, in rs370668897; 1 nsSNPs showed deleterious according to proven prediction and damaging sift prediction, in rs371745827; 6 nsSNPs showed deleterious by proven prediction and all of them were damaging by sift prediction, in rs371999153; 1nsSNPs showed deleterious by proven prediction and damaging by sift prediction, in rs372752293; 2 nsSNPs showed deleterious according to proven and damaging by sift prediction, in rs374222815; 1 nsSNPs showed neutral by proven prediction and damaging according to sift prediction, in rs374879205; 5 nsSNPs showed deleterious according to proven prediction, with damaging sift prediction for all five, in rs375020232, proven prediction showed 6 nsSNPs with deleterious predict and damaging predicts by sift prediction, in rs375164425; 2 nsSNPs showed neutral predict by proven and tolerated predicts by sift prediction.

In rs375553851; 4 nsSNPs showed neutral predicts by proven prediction but 1 nsSNPs deleterious predict while the forth were had damaging predicts by sift prediction, another rs375640863; showed 4 nsSNPs with deleterious predicts by proven predict and damaging by sift prediction, in rs377024581; according to proven prediction 1nsSNPs showed deleterious predict with damaging sift prediction, rs377266054; proven prediction showed 2 nsSNPs with neutral predicts in addition to damaging sift prediction and the last one rs377603311; showed 4 nsSNPs with deleterious predicts by proven prediction and 1 nsSNPs with neutral predict while sift prediction showed damaging for all ([Table 1](#)).

### Sift prediction

A total numbers of 127 out of 143 nsSNPs were considered deleterious by sift prediction in addition to 15 other snSNPs that was also deleterious too but they excluded from this study due to they considered benign according to polyphen-2 software with 1 snSNPs in rs188947672 at position L155V which represented the only SNPs that showed tolerated prediction by sift ([Table 2](#)).

Table 1: Illustrate proven prediction with sift results for SNPs.

SNP	Organism	Amino Acid Change	Proven Prediction Score	Proven Prediction (Cutoff=-2.5)	Proven #SEQ	Sift Score	Sift Prediction (Cutoff=0.05)
rs1145232	Homo_sapiens /GRCh37.74	G286R	-3.96	Deleterious	125	0	Damaging
rs1145232	Homo_sapiens /GRCh37.74	G325R	-5.21	Deleterious	95	0	Damaging
rs1145232	Homo_sapiens /GRCh37.74	G440R	-5.62	Deleterious	94	0	Damaging
rs1145232	Homo_sapiens /GRCh37.74	G501R	-5.49	Deleterious	94	0	Damaging
rs1145232	Homo_sapiens /GRCh37.74	G462R	-5.5	Deleterious	93	0	Damaging
rs5742973	Homo_sapiens /GRCh37.74	E27Q	-2.83	Deleterious	93	0	Damaging
rs56309301	Homo_sapiens /GRCh37.74	N243T	-1.88	Neutral	84	0.259	Tolerated
rs61756360	Homo_sapiens /GRCh37.74	T75I	-5.9	Deleterious	93	0	Damaging
rs111254723	Homo_sapiens /GRCh37.74	Y550C	-0.73	Neutral	125	0.08	Tolerated
rs111254723	Homo_sapiens /GRCh37.74	Y751C	-0.59	Neutral	95	0.061	Tolerated
rs111254723	Homo_sapiens /GRCh37.74	Y888C	-0.57	Neutral	93	0.065	Tolerated
rs111254723	Homo_sapiens /GRCh37.74	Y927C	-0.57	Neutral	92	0.064	Tolerated
rs142159998	Homo_sapiens /GRCh37.74	R721C	-4.46	Deleterious	94	0	Damaging
rs142159998	Homo_sapiens /GRCh37.74	R844C	-4.91	Deleterious	93	0.039	Damaging
rs142159998	Homo_sapiens /GRCh37.74	R883C	-4.87	Deleterious	92	0.039	Damaging
rs143010673	Homo_sapiens /GRCh37.74	W22C	-10.28	Deleterious	95	0.001	Damaging
rs143010673	Homo_sapiens /GRCh37.74	W137C	-10.66	Deleterious	94	0.001	Damaging
rs143010673	Homo_sapiens /GRCh37.74	W198C	-10.93	Deleterious	92	0.001	Damaging
rs143554211	Homo_sapiens /GRCh37.74	R695C	-1.23	Neutral	95	0.03	Damaging
rs143554211	Homo_sapiens /GRCh37.74	R494C	-1.35	Neutral	125	0.028	Damaging
rs143554211	Homo_sapiens /GRCh37.74	R259C	-1.8	Neutral	84	0.018	Damaging
rs143554211	Homo_sapiens /GRCh37.74	R832C	-1.38	Neutral	93	0.02	Damaging
rs143554211	Homo_sapiens /GRCh37.74	R871C	-1.34	Neutral	92	0.019	Damaging
rs143554211	Homo_sapiens /GRCh37.74	R709C	-1.24	Neutral	94	0.028	Damaging
rs143686298	Homo_sapiens /GRCh37.74	P732T	-1.75	Neutral	93	0.044	Damaging
rs143686298	Homo_sapiens /GRCh37.74	P771T	-1.75	Neutral	92	0.036	Damaging
rs145103030	Homo_sapiens /GRCh37.74	R542C	-5.3	Deleterious	125	0.007	Damaging
rs145103030	Homo_sapiens /GRCh37.74	R880C	-4.11	Deleterious	93	0.001	Damaging
rs145103030	Homo_sapiens /GRCh37.74	R743C	-4.82	Deleterious	95	0.001	Damaging

rs145103030	Homo_sapiens /GRCh37.74	R919C	-4.15	Deleterious	92	0.001	Damaging
rs145103030	Homo_sapiens /GRCh37.74	R757C	-3.4	Deleterious	94	0.004	Damaging
rs145521752	Homo_sapiens /GRCh37.74	E813A	-3.73	Deleterious	93	0.007	Damaging
rs145521752	Homo_sapiens /GRCh37.74	E852A	-3.73	Deleterious	92	0.007	Damaging
rs145521752	Homo_sapiens /GRCh37.74	E690A	-3.51	Deleterious	94	0	Damaging
rs145521752	Homo_sapiens /GRCh37.74	E676A	-4.02	Deleterious	95	0	Damaging
rs145521752	Homo_sapiens /GRCh37.74	E475A	-4.84	Deleterious	125	0	Damaging
rs145521752	Homo_sapiens /GRCh37.74	E240A	-4.7	Deleterious	84	0.006	Damaging
rs147901996	Homo_sapiens /GRCh37.74	N145S	-3.55	Deleterious	95	0.02	Damaging
rs147901996	Homo_sapiens /GRCh37.74	N106S	-3.38	Deleterious	125	0.02	Damaging
rs147901996	Homo_sapiens /GRCh37.74	N260S	-2.98	Deleterious	94	0.017	Damaging
rs148745528	Homo_sapiens /GRCh37.74	K99E	-3.77	Deleterious	125	0	Damaging
rs148745528	Homo_sapiens /GRCh37.74	K138E	-3.61	Deleterious	95	0	Damaging
rs148745528	Homo_sapiens /GRCh37.74	K253E	-3.38	Deleterious	94	0	Damaging
rs148745528	Homo_sapiens /GRCh37.74	K275E	-3.7	Deleterious	93	0	Damaging
rs148745528	Homo_sapiens /GRCh37.74	K314E	-3.47	Deleterious	92	0	Damaging
rs185306467	Homo_sapiens /GRCh37.74	I21N	-4.98	Deleterious	95	0.001	Damaging
rs185306467	Homo_sapiens /GRCh37.74	I136N	-5.74	Deleterious	94	0.001	Damaging
rs185306467	Homo_sapiens /GRCh37.74	I197N	-6.01	Deleterious	92	0.001	Damaging
rs188947672	Homo_sapiens /GRCh37.74	L706V	-0.9	Neutral	94	0.009	Damaging
rs188947672	Homo_sapiens /GRCh37.74	L728V	-1.1	Neutral	93	0.045	Damaging
rs188947672	Homo_sapiens /GRCh37.74	L591V	-1.25	Neutral	95	0.036	Damaging
rs188947672	Homo_sapiens /GRCh37.74	L155V	-1.35	Neutral	84	0.027	Damaging
rs189785572	Homo_sapiens /GRCh37.74	A501S	-0.81	Neutral	94	0.028	Damaging
rs189785572	Homo_sapiens /GRCh37.74	A386S	-0.89	Neutral	95	0.023	Damaging
rs193252599	Homo_sapiens /GRCh37.74	E168K	-1.7	Neutral	84	0.251	Tolerated
rs193252599	Homo_sapiens /GRCh37.74	E604K	-0.95	Neutral	95	0.014	Damaging
rs199892342	Homo_sapiens /GRCh37.74	V671A	-2.18	Neutral	95	0.002	Damaging
rs200172149	Homo_sapiens /GRCh37.74	T202A	-1.3	Neutral	84	0.06	Tolerated
rs200244068	Homo_sapiens /GRCh37.74	D106G	-4.65	Deleterious	94	0.004	Damaging
rs200244068	Homo_sapiens /GRCh37.74	D167G	-4.82	Deleterious	92	0.003	Damaging
rs200395679	Homo_sapiens /GRCh37.74	A104T	-2.37	Neutral	92	0.004	Damaging
rs200919195	Homo_sapiens /GRCh37.74	Y195F	-1.26	Neutral	84	0.204	Tolerated
rs201944922	Homo_sapiens /GRCh37.74	L4S	-5.37	Deleterious	93	0.001	Damaging

rs368282144	Homo_sapiens /GRCh37.74	P299A	-4.51	Deleterious	125	0	Damaging
rs368282144	Homo_sapiens /GRCh37.74	P338A	-3.74	Deleterious	95	0	Damaging
rs368282144	Homo_sapiens /GRCh37.74	P453A	-3.66	Deleterious	94	0	Damaging
rs368282144	Homo_sapiens /GRCh37.74	P514A	-4.22	Deleterious	94	0.094	Tolerated
rs368282144	Homo_sapiens /GRCh37.74	P475A	-4.1	Deleterious	93	0.144	Tolerated
rs369226504	Homo_sapiens /GRCh37.74	T202R	-3.15	Deleterious	84	0.006	Damaging
rs369226504	Homo_sapiens /GRCh37.74	T437R	-2.26	Neutral	125	0.013	Damaging
rs369226504	Homo_sapiens /GRCh37.74	T775R	-2.59	Deleterious	93	0.008	Damaging
rs369226504	Homo_sapiens /GRCh37.74	T638R	-2.37	Neutral	95	0.007	Damaging
rs369226504	Homo_sapiens /GRCh37.74	T814R	-2.79	Deleterious	92	0.008	Damaging
rs369226504	Homo_sapiens /GRCh37.74	T652R	-2.17	Neutral	94	0.011	Damaging
rs369814333	Homo_sapiens /GRCh37.74	N81I	-2.68	Deleterious	84	0.07	Tolerated
rs369814333	Homo_sapiens /GRCh37.74	N517I	-1.9	Neutral	95	0.071	Tolerated
rs369909997	Homo_sapiens /GRCh37.74	N228D	-1.16	Neutral	84	0.418	Tolerated
rs370084230	Homo_sapiens /GRCh37.74	R10Q	-2.57	Deleterious	94	0	Damaging
rs370300640	Homo_sapiens /GRCh37.74	G91S	-6	Deleterious	93	0	Damaging
rs370578519	Homo_sapiens /GRCh37.74	P661L	-4.41	Deleterious	93	0.003	Damaging
rs370578519	Homo_sapiens /GRCh37.74	P524L	-3.78	Deleterious	95	0.003	Damaging
rs370578519	Homo_sapiens /GRCh37.74	P700L	-4.38	Deleterious	92	0.003	Damaging
rs370578519	Homo_sapiens /GRCh37.74	P639L	-4.03	Deleterious	94	0.003	Damaging
rs370668897	Homo_sapiens /GRCh37.74	K51T	-4.09	Deleterious	94	0.003	Damaging
rs371745827	Homo_sapiens /GRCh37.74	R435C	-5.23	Deleterious	125	0	Damaging
rs371745827	Homo_sapiens /GRCh37.74	R773C	-4.84	Deleterious	93	0	Damaging
rs371745827	Homo_sapiens /GRCh37.74	R636C	-4.44	Deleterious	95	0	Damaging
rs371745827	Homo_sapiens /GRCh37.74	R812C	-5.11	Deleterious	92	0	Damaging
rs371745827	Homo_sapiens /GRCh37.74	R650C	-4.88	Deleterious	94	0	Damaging
rs371745827	Homo_sapiens /GRCh37.74	R200C	-6.48	Deleterious	84	0	Damaging
rs371999153	Homo_sapiens /GRCh37.74	W49C	-11.6	Deleterious	164	0	Damaging
rs372752293	Homo_sapiens /GRCh37.74	T110R	-5.74	Deleterious	93	0	Damaging
rs372752293	Homo_sapiens /GRCh37.74	T49R	-5.48	Deleterious	94	0	Damaging
rs374222815	Homo_sapiens /GRCh37.74	V505M	-1.48	Neutral	125	0	Damaging
rs374222815	Homo_sapiens /GRCh37.74	V706M	-1.81	Neutral	95	0	Damaging
rs374222815	Homo_sapiens /GRCh37.74	V843M	-1.88	Neutral	93	0.003	Damaging
rs374222815	Homo_sapiens /GRCh37.74	V882M	-1.81	Neutral	92	0.002	Damaging

rs374222815	Homo_sapiens /GRCh37.74	V720M	-1.52	Neutral	94	0	Damaging
rs374879205	Homo_sapiens /GRCh37.74	P512A	-3.12	Deleterious	125	0	Damaging
rs374879205	Homo_sapiens /GRCh37.74	P713A	-3.57	Deleterious	95	0.013	Damaging
rs374879205	Homo_sapiens /GRCh37.74	P850A	-3.79	Deleterious	93	0	Damaging
rs374879205	Homo_sapiens /GRCh37.74	P889A	-3.75	Deleterious	92	0.014	Damaging
rs374879205	Homo_sapiens /GRCh37.74	P727A	-3.24	Deleterious	94	0.025	Damaging
rs375020232	Homo_sapiens /GRCh37.74	R435L	-3.67	Deleterious	125	0	Damaging
rs375020232	Homo_sapiens /GRCh37.74	R773L	-4.39	Deleterious	93	0	Damaging
rs375020232	Homo_sapiens /GRCh37.74	R636L	-4.12	Deleterious	95	0	Damaging
rs375020232	Homo_sapiens /GRCh37.74	R812L	-4.56	Deleterious	92	0	Damaging
rs375020232	Homo_sapiens /GRCh37.74	R650L	-4.15	Deleterious	94	0	Damaging
rs375020232	Homo_sapiens /GRCh37.74	R200L	-5.43	Deleterious	84	0	Damaging
rs375164425	Homo_sapiens /GRCh37.74	I57V	-0.48	Neutral	125	0.127	Tolerated
rs375164425	Homo_sapiens /GRCh37.74	I96V	-0.65	Neutral	95	0.137	Tolerated
rs375553851	Homo_sapiens /GRCh37.74	N703H	-1.98	Neutral	94	0.005	Damaging
rs375553851	Homo_sapiens /GRCh37.74	N152H	-2.93	Deleterious	84	0.01	Damaging
rs375553851	Homo_sapiens /GRCh37.74	N588H	-2.17	Neutral	95	0.005	Damaging
rs375553851	Homo_sapiens /GRCh37.74	N725H	-2.16	Neutral	93	0.012	Damaging
rs375553851	Homo_sapiens /GRCh37.74	N764H	-2.23	Neutral	92	0.012	Damaging
rs375640863	Homo_sapiens /GRCh37.74	D435G	-3.14	Deleterious	94	0.004	Damaging
rs375640863	Homo_sapiens /GRCh37.74	D281G	-2.9	Deleterious	125	0.004	Damaging
rs375640863	Homo_sapiens /GRCh37.74	D320G	-3.01	Deleterious	95	0.004	Damaging
rs375640863	Homo_sapiens /GRCh37.74	D457G	-3.22	Deleterious	93	0.003	Damaging
rs377024581	Homo_sapiens /GRCh37.74	D56G	-6.83	Deleterious	93	0	Damaging
rs377266054	Homo_sapiens /GRCh37.74	E511V	-2.42	Neutral	95	0.01	Damaging
rs377266054	Homo_sapiens /GRCh37.74	E626V	-2.11	Neutral	94	0.008	Damaging
rs377603311	Homo_sapiens /GRCh37.74	R844H	-2.92	Deleterious	93	0.003	Damaging
rs377603311	Homo_sapiens /GRCh37.74	R883H	-2.96	Deleterious	92	0.003	Damaging
rs377603311	Homo_sapiens /GRCh37.74	R721H	-2.11	Neutral	94	0	Damaging
rs377603311	Homo_sapiens /GRCh37.74	R707H	-3.3	Deleterious	95	0.003	Damaging
rs377603311	Homo_sapiens /GRCh37.74	R506H	-3.59	Deleterious	125	0	Damaging

Table 2: Illustrate SNPs predictions results by SIFT and polyphen-2 prediction tools.

SNP	Organism	Amino Acid Change	Sift Score	Sift Prediction	Polyphen Result	Polyphen Score
rs1145232	Homo_sapiens /GRCh37.74	G286R	0	DELETERIOUS	PROBABLY DAMAGING	1
rs1145232	Homo_sapiens /GRCh37.74	G325R	0	DELETERIOUS	-	-
rs1145232	Homo_sapiens /GRCh37.74	G440R	0	DELETERIOUS	PROBABLY DAMAGING	1
rs1145232	Homo_sapiens /GRCh37.74	G501R	0	DELETERIOUS	PROBABLY DAMAGING	1
rs1145232	Homo_sapiens /GRCh37.74	G462R	0.002	DELETERIOUS	PROBABLY DAMAGING	1
rs5742973	Homo_sapiens /GRCh37.74	E27Q	0	DELETERIOUS	PROBABLY DAMAGING	1
rs56309301	Homo_sapiens /GRCh37.74	N243T	0.011	DELETERIOUS	POSSIBLY DAMAGING	0.873
rs61756360	Homo_sapiens /GRCh37.74	T75I	0	DELETERIOUS	PROBABLY DAMAGING	1
rs111254723	Homo_sapiens /GRCh37.74	Y550C	0.037	DELETERIOUS	POSSIBLY DAMAGING	0.899
rs111254723	Homo_sapiens /GRCh37.74	Y751C	0.041	DELETERIOUS	-	-
rs111254723	Homo_sapiens /GRCh37.74	Y888C	0.046	DELETERIOUS	POSSIBLY DAMAGING	0.898
rs111254723	Homo_sapiens /GRCh37.74	Y927C	0.048	DELETERIOUS	POSSIBLY DAMAGING	0.833
rs142159998	Homo_sapiens /GRCh37.74	R721C	0.038	DELETERIOUS	POSSIBLY DAMAGING	0.655
rs142159998	Homo_sapiens /GRCh37.74	R844C	0.04	DELETERIOUS	PROBABLY DAMAGING	0.997
rs142159998	Homo_sapiens /GRCh37.74	R883C	0.04	DELETERIOUS	PROBABLY DAMAGING	0.995
rs143010673	Homo_sapiens /GRCh37.74	W22C	0	DELETERIOUS	-	-
rs143010673	Homo_sapiens /GRCh37.74	W137C	0.001	DELETERIOUS	POSSIBLY DAMAGING	0.79
rs143010673	Homo_sapiens /GRCh37.74	W198C	0.002	DELETERIOUS	PROBABLY DAMAGING	1
rs143554211	Homo_sapiens /GRCh37.74	R695C	0.019	DELETERIOUS	-	-
rs143554211	Homo_sapiens /GRCh37.74	R494C	0.02	DELETERIOUS	PROBABLY DAMAGING	1
rs143554211	Homo_sapiens /GRCh37.74	R259C	0.021	DELETERIOUS	PROBABLY DAMAGING	0.999
rs143554211	Homo_sapiens /GRCh37.74	R832C	0.032	DELETERIOUS	PROBABLY DAMAGING	0.999
rs143554211	Homo_sapiens /GRCh37.74	R871C	0.032	DELETERIOUS	PROBABLY DAMAGING	0.999
rs143554211	Homo_sapiens /GRCh37.74	R709C	0.033	DELETERIOUS	PROBABLY DAMAGING	1
rs143686298	Homo_sapiens /GRCh37.74	P732T	0.022	DELETERIOUS	POSSIBLY DAMAGING	0.555
rs143686298	Homo_sapiens /GRCh37.74	P771T	0.023	DELETERIOUS	POSSIBLY DAMAGING	0.555
rs145103030	Homo_sapiens /GRCh37.74	R542C	0.001	DELETERIOUS	PROBABLY DAMAGING	1
rs145103030	Homo_sapiens /GRCh37.74	R880C	0.001	DELETERIOUS	PROBABLY DAMAGING	1
rs145103030	Homo_sapiens /GRCh37.74	R743C	0.001	DELETERIOUS	-	-
rs145103030	Homo_sapiens /GRCh37.74	R919C	0.001	DELETERIOUS	PROBABLY DAMAGING	1
rs145103030	Homo_sapiens /GRCh37.74	R757C	0.001	DELETERIOUS	PROBABLY DAMAGING	1
rs145521752	Homo_sapiens /GRCh37.74	E813A	0.006	DELETERIOUS	PROBABLY DAMAGING	0.965

rs145521752	Homo_sapiens /GRCh37.74	E852A	0.006	DELETERIOUS	POSSIBLY DAMAGING	0.939
rs145521752	Homo_sapiens /GRCh37.74	E690A	0.007	DELETERIOUS	PROBABLY DAMAGING	1
rs145521752	Homo_sapiens /GRCh37.74	E676A	0.008	DELETERIOUS	-	-
rs145521752	Homo_sapiens /GRCh37.74	E475A	0.01	DELETERIOUS	PROBABLY DAMAGING	0.978
rs145521752	Homo_sapiens /GRCh37.74	E240A	0.013	DELETERIOUS	PROBABLY DAMAGING	1
rs147901996	Homo_sapiens /GRCh37.74	N145S	0.031	DELETERIOUS	-	-
rs147901996	Homo_sapiens /GRCh37.74	N106S	0.035	DELETERIOUS	POSSIBLY DAMAGING	0.932
rs147901996	Homo_sapiens /GRCh37.74	N260S	0.043	DELETERIOUS	POSSIBLY DAMAGING	0.719
rs148745528	Homo_sapiens /GRCh37.74	K99E	0	DELETERIOUS	PROBABLY DAMAGING	1.000
rs148745528	Homo_sapiens /GRCh37.74	K138E	0	DELETERIOUS	-	-
rs148745528	Homo_sapiens /GRCh37.74	K253E	0	DELETERIOUS	PROBABLY DAMAGING	1
rs148745528	Homo_sapiens /GRCh37.74	K275E	0.003	DELETERIOUS	PROBABLY DAMAGING	1
rs148745528	Homo_sapiens /GRCh37.74	K314E	0.003	DELETERIOUS	PROBABLY DAMAGING	1
rs185306467	Homo_sapiens /GRCh37.74	I21N	0.002	DELETERIOUS	-	-
rs185306467	Homo_sapiens /GRCh37.74	I136N	0.002	DELETERIOUS	POSSIBLY DAMAGING	0.938
rs185306467	Homo_sapiens /GRCh37.74	I197N	0.002	DELETERIOUS	POSSIBLY DAMAGING	0.892
rs188947672	Homo_sapiens /GRCh37.74	L706V	0.016	DELETERIOUS	POSSIBLY DAMAGING	0.926
rs188947672	Homo_sapiens /GRCh37.74	L728V	0.033	DELETERIOUS	POSSIBLY DAMAGING	0.926
rs188947672	Homo_sapiens /GRCh37.74	L591V	0.036	DELETERIOUS	-	-
rs188947672	Homo_sapiens /GRCh37.74	L155V	0.206	TOLERATED	POSSIBLY DAMAGING	0.944
rs189785572	Homo_sapiens /GRCh37.74	A501S	0.024	DELETERIOUS	PROBABLY DAMAGING	0.987
rs189785572	Homo_sapiens /GRCh37.74	A386S	0.03	DELETERIOUS	-	-
rs193252599	Homo_sapiens /GRCh37.74	E168K	0.017	DELETERIOUS	POSSIBLY DAMAGING	0.868
rs193252599	Homo_sapiens /GRCh37.74	E604K	0.039	DELETERIOUS	-	-
rs199892342	Homo_sapiens /GRCh37.74	V671A	0.029	DELETERIOUS	-	-
rs200172149	Homo_sapiens /GRCh37.74	T202A	0.035	DELETERIOUS	POSSIBLY DAMAGING	0.604
rs200244068	Homo_sapiens /GRCh37.74	D106G	0.005	DELETERIOUS	POSSIBLY DAMAGING	0.787
rs200244068	Homo_sapiens /GRCh37.74	D167G	0.006	DELETERIOUS	POSSIBLY DAMAGING	0.885
rs200395679	Homo_sapiens /GRCh37.74	A104T	0.006	DELETERIOUS	PROBABLY DAMAGING	0.997
rs200919195	Homo_sapiens /GRCh37.74	Y195F	0	DELETERIOUS	POSSIBLY DAMAGING	0.782
rs201944922	Homo_sapiens /GRCh37.74	L4S	0	DELETERIOUS	PROBABLY DAMAGING	1
rs368282144	Homo_sapiens /GRCh37.74	P299A	0	DELETERIOUS	PROBABLY DAMAGING	0.997



rs368282144	Homo_sapiens /GRCh37.74	P338A	0	DELETERIOUS	-	-
rs368282144	Homo_sapiens /GRCh37.74	P453A	0	DELETERIOUS	PROBABLY DAMAGING	1
rs368282144	Homo_sapiens /GRCh37.74	P514A	0	DELETERIOUS	PROBABLY DAMAGING	0.995
rs368282144	Homo_sapiens /GRCh37.74	P475A	0.012	DELETERIOUS	PROBABLY DAMAGING	0.995
rs369226504	Homo_sapiens /GRCh37.74	T202R	0.004	DELETERIOUS	PROBABLY DAMAGING	0.988
rs369226504	Homo_sapiens /GRCh37.74	T437R	0.01	DELETERIOUS	POSSIBLY DAMAGING	0.82
rs369226504	Homo_sapiens /GRCh37.74	T775R	0.011	DELETERIOUS	PROBABLY DAMAGING	0.997
rs369226504	Homo_sapiens /GRCh37.74	T638R	0.012	DELETERIOUS	PROBABLY DAMAGING	0.999
rs369226504	Homo_sapiens /GRCh37.74	T814R	0.012	DELETERIOUS	PROBABLY DAMAGING	0.994
rs369226504	Homo_sapiens /GRCh37.74	T652R	0.013	DELETERIOUS	POSSIBLY DAMAGING	0.956
rs369814333	Homo_sapiens /GRCh37.74	N81I	0.026	DELETERIOUS	POSSIBLY DAMAGING	0.730
rs369814333	Homo_sapiens /GRCh37.74	N517I	0.046	DELETERIOUS	-	-
rs369909997	Homo_sapiens /GRCh37.74	N228D	0.049	DELETERIOUS	POSSIBLY DAMAGING	0.925
rs370084230	Homo_sapiens /GRCh37.74	R10Q	0.008	DELETERIOUS	PROBABLY DAMAGING	1
rs370300640	Homo_sapiens /GRCh37.74	G91S	0	DELETERIOUS	PROBABLY DAMAGING	1
rs370578519	Homo_sapiens /GRCh37.74	P661L	0.004	DELETERIOUS	PROBABLY DAMAGING	0.979
rs370578519	Homo_sapiens /GRCh37.74	P524L	0.004	DELETERIOUS	PROBABLY DAMAGING	0.979
rs370578519	Homo_sapiens /GRCh37.74	P700L	0.004	DELETERIOUS	POSSIBLY DAMAGING	0.945
rs370578519	Homo_sapiens /GRCh37.74	P639L	0.009	DELETERIOUS	PROBABLY DAMAGING	0.989
rs370668897	Homo_sapiens /GRCh37.74	K51T	0.021	DELETERIOUS	PROBABLY DAMAGING	0.970
rs371745827	Homo_sapiens /GRCh37.74	R435C	0	DELETERIOUS	PROBABLY DAMAGING	1.000
rs371745827	Homo_sapiens /GRCh37.74	R773C	0	DELETERIOUS	PROBABLY DAMAGING	1
rs371745827	Homo_sapiens /GRCh37.74	R636C	0	DELETERIOUS	-	-
rs371745827	Homo_sapiens /GRCh37.74	R812C	0	DELETERIOUS	PROBABLY DAMAGING	1
rs371745827	Homo_sapiens /GRCh37.74	R650C	0	DELETERIOUS	PROBABLY DAMAGING	1
rs371745827	Homo_sapiens /GRCh37.74	R200C	0	DELETERIOUS	PROBABLY DAMAGING	1
rs371999153	Homo_sapiens /GRCh37.74	W49C	0.002	DELETERIOUS	PROBABLY DAMAGING	1
rs372752293	Homo_sapiens /GRCh37.74	T110R	0.001	DELETERIOUS	PROBABLY DAMAGING	1
rs372752293	Homo_sapiens /GRCh37.74	T49R	0.001	DELETERIOUS	PROBABLY DAMAGING	1
rs374222815	Homo_sapiens /GRCh37.74	V505M	0	DELETERIOUS	PROBABLY DAMAGING	1
rs374222815	Homo_sapiens /GRCh37.74	V706M	0	DELETERIOUS	PROBABLY DAMAGING	1
rs374222815	Homo_sapiens /GRCh37.74	V843M	0.003	DELETERIOUS	PROBABLY DAMAGING	1
rs374222815	Homo_sapiens /GRCh37.74	V882M	0.003	DELETERIOUS	PROBABLY DAMAGING	1
rs374222815	Homo_sapiens /GRCh37.74	V720M	0.004	DELETERIOUS	PROBABLY DAMAGING	1

rs374879205	Homo_sapiens /GRCh37.74	P512A	0	DELETERIOUS	PROBABLY DAMAGING	0.997
rs374879205	Homo_sapiens /GRCh37.74	P713A	0	DELETERIOUS	PROBABLY DAMAGING	1
rs374879205	Homo_sapiens /GRCh37.74	P850A	0.015	DELETERIOUS	PROBABLY DAMAGING	1
rs374879205	Homo_sapiens /GRCh37.74	P889A	0.015	DELETERIOUS	PROBABLY DAMAGING	1
rs374879205	Homo_sapiens /GRCh37.74	P727A	0.016	DELETERIOUS	PROBABLY DAMAGING	1
rs375020232	Homo_sapiens /GRCh37.74	R435L	0	DELETERIOUS	PROBABLY DAMAGING	1
rs375020232	Homo_sapiens /GRCh37.74	R773L	0	DELETERIOUS	PROBABLY DAMAGING	1
rs375020232	Homo_sapiens /GRCh37.74	R636L	0	DELETERIOUS	PROBABLY DAMAGING	1
rs375020232	Homo_sapiens /GRCh37.74	R812L	0	DELETERIOUS	PROBABLY DAMAGING	1
rs375020232	Homo_sapiens /GRCh37.74	R650L	0	DELETERIOUS	PROBABLY DAMAGING	1
rs375020232	Homo_sapiens /GRCh37.74	R200L	0	DELETERIOUS	PROBABLY DAMAGING	1
rs375164425	Homo_sapiens /GRCh37.74	I57V	0	DELETERIOUS	POSSIBLY DAMAGING	0.926
rs375164425	Homo_sapiens /GRCh37.74	I96V	0	DELETERIOUS	PROBABLY DAMAGING	1
rs375553851	Homo_sapiens /GRCh37.74	N703H	0.005	DELETERIOUS	PROBABLY DAMAGING	1
rs375553851	Homo_sapiens /GRCh37.74	N152H	0.008	DELETERIOUS	PROBABLY DAMAGING	0.988
rs375553851	Homo_sapiens /GRCh37.74	N588H	0.021	DELETERIOUS	PROBABLY DAMAGING	0.997
rs375553851	Homo_sapiens /GRCh37.74	N725H	0.022	DELETERIOUS	PROBABLY DAMAGING	0.997
rs375553851	Homo_sapiens /GRCh37.74	N764H	0.022	DELETERIOUS	PROBABLY DAMAGING	0.996
rs375640863	Homo_sapiens /GRCh37.74	D435G	0.004	DELETERIOUS	PROBABLY DAMAGING	0.998
rs375640863	Homo_sapiens /GRCh37.74	D281G	0.005	DELETERIOUS	PROBABLY DAMAGING	0.992
rs375640863	Homo_sapiens /GRCh37.74	D320G	0.005	DELETERIOUS	PROBABLY DAMAGING	0.998
rs375640863	Homo_sapiens /GRCh37.74	D457G	0.024	DELETERIOUS	PROBABLY DAMAGING	0.985
rs377024581	Homo_sapiens /GRCh37.74	D56G	0	DELETERIOUS	PROBABLY DAMAGING	1
rs377266054	Homo_sapiens /GRCh37.74	E511V	0.038	DELETERIOUS	PROBABLY DAMAGING	0.998
rs377266054	Homo_sapiens /GRCh37.74	E626V	0.045	DELETERIOUS	PROBABLY DAMAGING	0.999
rs377603311	Homo_sapiens /GRCh37.74	R844H	0.003	DELETERIOUS	PROBABLY DAMAGING	1
rs377603311	Homo_sapiens /GRCh37.74	R883H	0.003	DELETERIOUS	PROBABLY DAMAGING	1
rs377603311	Homo_sapiens /GRCh37.74	R721H	0.003	DELETERIOUS	PROBABLY DAMAGING	1
rs377603311	Homo_sapiens /GRCh37.74	R707H	0.005	DELETERIOUS	PROBABLY DAMAGING	1
rs377603311	Homo_sapiens /GRCh37.74	R506H	0.007	DELETERIOUS	PROBABLY DAMAGING	1

Note: - Indicate misinformation.

### Polyphen-2

The Polyphen-2 results showed 85 nsSNPs out of 143 nsSNPs as probably damaging, while 27 nsSNPs showed possibly damaging with 16 nsSNPs that showed no results; they are (rs1145232/ rs111254723/ rs143010673/ rs143554211/ rs145103030/ rs145521752/ rs147901996 / rs148745528 / rs185306467/ rs188947672/ rs189785572/ rs193252599/ rs199892342/ rs368282144/ rs369226504/ rs369814333/ rs370578519/ rs371745827/ rs374222815/ rs374879205/ rs375020232/ rs375164425/ rs375553851/ rs375640863/ rs377266054/ rs377603311 at the following positions: G325R, Y751C, R721C, W22C, R695C, R743C, E676A, N145S, K138E, I21N, L591V, A386S, E604K, V671A, P338A, T638R, N517I, P524L, R636C, V706M, P713A, R636L, I96V, N588H, D320G, E511V, R707H, with ENSP00000404492 protein ID ); may be due to some sequence problems or even the software and 15 nsSNPs that were considered benign which was excluded from this study (Table 2).

### I Mutant suit

According to I mutant suite-3 results I found 103 snSNPs

showed decreased in protein functionality within these 103 snSNPs; 14 snSNPs were considered benign by polyphen-2 and should be excluded from this study in addition 14 snSNPs showed increased in protein functionality while 26 snSNPs were not showed any results (Table 3).

### SNPs and GO

According to SNPs & GO prediction I showed the following results:-

PhD-SNP prediction results showed 70 snSNPs predicted as disease in addition to other 9 nsSNPs that were excluded due to they gave benign by Polyphen-2, 32 nsSNPs considered neutral in addition to other 6 snSNPs which was considered benign according to Polyphen-2 and excluded from this study too while 26 snSNPs that showed no prediction results.

SNPS & GO prediction showed 53 snSNPs that predicted as disease and 49 snSNPs as neutral in addition to 15 snSNPs that

Table 3: Illustrate I mutant suite 3 results.

SNP	Organism	Amino Acid Change	WT	MT	DDG	RI	I Mutant Result
rs1145232	Homo_sapiens /GRCh37.74	G286R	G	R	-0.71	7	Decrease
rs1145232	Homo_sapiens /GRCh37.74	G325R					
rs1145232	Homo_sapiens /GRCh37.74	G440R	G	R	-0.71	7	Decrease
rs1145232	Homo_sapiens /GRCh37.74	G501R	G	R	-0.32	2	Decrease
rs1145232	Homo_sapiens /GRCh37.74	G462R	G	R	-0.71	7	Decrease
rs5742973	Homo_sapiens /GRCh37.74	E27Q	E	Q	-0.86	9	Decrease
rs56309301	Homo_sapiens /GRCh37.74	N243T	N	T	0.25	3	Increase
rs61756360	Homo_sapiens /GRCh37.74	T75I	T	I	-0.35	2	Decrease
rs111254723	Homo_sapiens /GRCh37.74	Y550C	Y	C	-0.95	0	Increase
rs111254723	Homo_sapiens /GRCh37.74	Y751C	-	-	-	-	-
rs111254723	Homo_sapiens /GRCh37.74	Y888C	Y	C	-0.95	0	Increase
rs111254723	Homo_sapiens /GRCh37.74	Y927C	Y	C	-0.95	0	Increase
rs142159998	Homo_sapiens /GRCh37.74	R721C	R	C	-1.02	5	Decrease
rs142159998	Homo_sapiens /GRCh37.74	R844C	R	C	-1.02	5	Decrease
rs142159998	Homo_sapiens /GRCh37.74	R883C	R	C	-1.02	5	Decrease
rs143010673	Homo_sapiens /GRCh37.74	W22C	-	-	-	-	-
rs143010673	Homo_sapiens /GRCh37.74	W137C	W	C	-1.53	8	Decrease
rs143010673	Homo_sapiens /GRCh37.74	W198C	W	C	-1.53	8	Decrease
rs143554211	Homo_sapiens /GRCh37.74	R695C	-	-	-	-	-
rs143554211	Homo_sapiens /GRCh37.74	R494C	R	C	-1.06	5	Decrease
rs143554211	Homo_sapiens /GRCh37.74	R259C	R	C	-1.09	6	Decrease
rs143554211	Homo_sapiens /GRCh37.74	R832C	R	C	-1.06	5	Decrease

rs143554211	Homo_sapiens /GRCh37.74	R871C	R	C	-1.06	5	Decrease
rs143554211	Homo_sapiens /GRCh37.74	R709C	R	C	-1.06	5	Decrease
rs143686298	Homo_sapiens /GRCh37.74	P732T	P	T	-0.83	6	Decrease
rs143686298	Homo_sapiens /GRCh37.74	P771T	P	T	-0.83	6	Decrease
rs145103030	Homo_sapiens /GRCh37.74	R542C	R	C	-0.97	4	Decrease
rs145103030	Homo_sapiens /GRCh37.74	R880C	R	C	-0.97	4	Decrease
rs145103030	Homo_sapiens /GRCh37.74	R743C	-	-	-	-	-
rs145103030	Homo_sapiens /GRCh37.74	R919C	R	C	-0.97	4	Decrease
rs145103030	Homo_sapiens /GRCh37.74	R757C	R	C	-0.97	4	Decrease
rs145521752	Homo_sapiens /GRCh37.74	E813A	E	A	-0.67	6	Decrease
rs145521752	Homo_sapiens /GRCh37.74	E852A	E	A	-0.67	6	Decrease
rs145521752	Homo_sapiens /GRCh37.74	E690A	E	A	-0.67	6	Decrease
rs145521752	Homo_sapiens /GRCh37.74	E676A	-	-	-	-	-
rs145521752	Homo_sapiens /GRCh37.74	E475A	E	A	-0.67	6	Decrease
rs145521752	Homo_sapiens /GRCh37.74	E240A	E	A	-0.67	6	Decrease
rs147901996	Homo_sapiens /GRCh37.74	N145S	-	-	-	-	-
rs147901996	Homo_sapiens /GRCh37.74	N106S	N	S	-0.24	6	Decrease
rs147901996	Homo_sapiens /GRCh37.74	N260S	N	S	-0.24	6	Decrease
rs148745528	Homo_sapiens /GRCh37.74	K99E	K	E	-0.19	1	Increase
rs148745528	Homo_sapiens /GRCh37.74	K138E	-	-	-	-	-
rs148745528	Homo_sapiens /GRCh37.74	K253E	K	E	-0.19	1	Increase
rs148745528	Homo_sapiens /GRCh37.74	K275E	K	E	-0.19	1	Increase
rs148745528	Homo_sapiens /GRCh37.74	K314E	K	E	-0.19	1	Increase
rs185306467	Homo_sapiens /GRCh37.74	I21N	-	-	-	-	-
rs185306467	Homo_sapiens /GRCh37.74	I136N	I	N	-1.84	6	Decrease
rs185306467	Homo_sapiens /GRCh37.74	I197N	I	N	-1.84	6	Decrease
rs188947672	Homo_sapiens /GRCh37.74	L706V	L	V	-1.48	7	Decrease
rs188947672	Homo_sapiens /GRCh37.74	L728V	L	V	-1.47	7	Decrease
rs188947672	Homo_sapiens /GRCh37.74	L591V					
rs188947672	Homo_sapiens /GRCh37.74	L155V	L	V	-1.47	7	Decrease
rs189785572	Homo_sapiens /GRCh37.74	A501S	A	S	-1.02	9	Decrease
rs189785572	Homo_sapiens /GRCh37.74	A386S					
rs193252599	Homo_sapiens /GRCh37.74	E168K	E	K	-0.6	6	Decrease
rs193252599	Homo_sapiens /GRCh37.74	E604K					

rs199892342	Homo_sapiens /GRCh37.74	V671A					
rs200172149	Homo_sapiens /GRCh37.74	T202A	T	A	-1.69	9	Decrease
rs200244068	Homo_sapiens /GRCh37.74	D106G	D	G	-0.75	5	Decrease
rs200244068	Homo_sapiens /GRCh37.74	D167G	D	G	-0.75	5	Decrease
rs200395679	Homo_sapiens /GRCh37.74	A104T	A	T	-0.56	5	Decrease
rs200919195	Homo_sapiens /GRCh37.74	Y195F	Y	F	-0.87	7	Decrease
rs201944922	Homo_sapiens /GRCh37.74	L4S	L	S	-2.31	9	Decrease
rs368282144	Homo_sapiens /GRCh37.74	P299A	P	A	-1.53	8	Decrease
rs368282144	Homo_sapiens /GRCh37.74	P338A					
rs368282144	Homo_sapiens /GRCh37.74	P453A	P	A	-1.53	8	Decrease
rs368282144	Homo_sapiens /GRCh37.74	P514A	P	A	-1.53	8	Decrease
rs368282144	Homo_sapiens /GRCh37.74	P475A	P	A	-1.53	8	Decrease
rs369226504	Homo_sapiens /GRCh37.74	T202R	T	R	-0.75	6	Decrease
rs369226504	Homo_sapiens /GRCh37.74	T437R	T	R	-0.75	6	Decrease
rs369226504	Homo_sapiens /GRCh37.74	T775R	T	R	-0.75	6	Decrease
rs369226504	Homo_sapiens /GRCh37.74	T638R					
rs369226504	Homo_sapiens /GRCh37.74	T814R	T	R	-0.75	6	Decrease
rs369226504	Homo_sapiens /GRCh37.74	T652R	T	R	-0.75	6	Decrease
rs369814333	Homo_sapiens /GRCh37.74	N81I	N	I	0.86	5	Increase
rs369814333	Homo_sapiens /GRCh37.74	N517I					
rs369909997	Homo_sapiens /GRCh37.74	N228D	N	D	-0.47	7	Decrease
rs370084230	Homo_sapiens /GRCh37.74	R10Q	R	Q	-0.76	5	Decrease
rs370300640	Homo_sapiens /GRCh37.74	G91S	G	S	-1.19	7	Decrease
rs370578519	Homo_sapiens /GRCh37.74	P661L	P	L	0.46	2	Increase
rs370578519	Homo_sapiens /GRCh37.74	P524L	-	-	-	-	-
rs370578519	Homo_sapiens /GRCh37.74	P700L	P	L	-0.46	2	Increase
rs370578519	Homo_sapiens /GRCh37.74	P639L	P	L	-0.46	2	Increase
rs370668897	Homo_sapiens /GRCh37.74	K51T	K	T	-0.54	3	Decrease
rs371745827	Homo_sapiens /GRCh37.74	R435C	R	C	-1.15	3	Decrease
rs371745827	Homo_sapiens /GRCh37.74	R773C	R	C	-1.15	3	Decrease
rs371745827	Homo_sapiens /GRCh37.74	R636C	-	-	-	-	-
rs371745827	Homo_sapiens /GRCh37.74	R812C	R	C	-1.15	3	Decrease
rs371745827	Homo_sapiens /GRCh37.74	R650C	R	C	-1.15	3	Decrease
rs371745827	Homo_sapiens /GRCh37.74	R200C	R	C	-1.15	3	Decrease

rs371999153	Homo_sapiens /GRCh37.74	W49C	W	C	-1.62	8	Decrease
rs372752293	Homo_sapiens /GRCh37.74	T110R	T	R	-0.46	4	Decrease
rs372752293	Homo_sapiens /GRCh37.74	T49R	T	R	-0.64	3	Decrease
rs374222815	Homo_sapiens /GRCh37.74	V505M	V	M	-1.32	8	Decrease
rs374222815	Homo_sapiens /GRCh37.74	V706M					
rs374222815	Homo_sapiens /GRCh37.74	V843M	V	M	-1.32	8	Decrease
rs374222815	Homo_sapiens /GRCh37.74	V882M	V	M	-1.32	8	Decrease
rs374222815	Homo_sapiens /GRCh37.74	V720M	V	M	-1.32	8	Decrease
rs374879205	Homo_sapiens /GRCh37.74	P512A	P	A	-1.27	6	Decrease
rs374879205	Homo_sapiens /GRCh37.74	P713A	-	-	-	-	-
rs374879205	Homo_sapiens /GRCh37.74	P850A	P	A	-1.27	6	Decrease
rs374879205	Homo_sapiens /GRCh37.74	P889A	P	A	-1.27	6	Decrease
rs374879205	Homo_sapiens /GRCh37.74	P727A	P	A	-1.27	6	Decrease
rs375020232	Homo_sapiens /GRCh37.74	R435L	R	L	-0.7	8	Decrease
rs375020232	Homo_sapiens /GRCh37.74	R773L	R	L	-0.7	8	Decrease
rs375020232	Homo_sapiens /GRCh37.74	R636L	-	-	-	-	-
rs375020232	Homo_sapiens /GRCh37.74	R812L	R	L	-0.7	8	Decrease
rs375020232	Homo_sapiens /GRCh37.74	R650L	R	L	-0.7	8	Decrease
rs375020232	Homo_sapiens /GRCh37.74	R200L	R	L	-0.7	8	Decrease
rs375164425	Homo_sapiens /GRCh37.74	I57V	I	V	-1.17	8	Decrease
rs375164425	Homo_sapiens /GRCh37.74	I96V	-	-	-	-	-
rs375553851	Homo_sapiens /GRCh37.74	N703H	N	H	-0.45	6	Decrease
rs375553851	Homo_sapiens /GRCh37.74	N152H	N	H	-0.45	6	Decrease
rs375553851	Homo_sapiens /GRCh37.74	N588H	-	-	-	-	-
rs375553851	Homo_sapiens /GRCh37.74	N725H	N	H	-0.45	6	Decrease
rs375553851	Homo_sapiens /GRCh37.74	N764H	N	H	-0.45	6	Decrease
rs375640863	Homo_sapiens /GRCh37.74	D435G	D	G	-1.22	1	Decrease
rs375640863	Homo_sapiens /GRCh37.74	D281G	D	G	-1.22	1	Decrease
rs375640863	Homo_sapiens /GRCh37.74	D320G	-	-	-	-	-
rs375640863	Homo_sapiens /GRCh37.74	D457G	D	G	-1.22	1	Decrease
rs377024581	Homo_sapiens /GRCh37.74	D56G	D	G	-1.27	3	Decrease
rs377266054	Homo_sapiens /GRCh37.74	E511V	-	-	-	-	-
rs377266054	Homo_sapiens /GRCh37.74	E626V	E	V	0.32	8	Increase
rs377603311	Homo_sapiens /GRCh37.74	R844H	R	H	-1.43	9	Decrease

rs377603311	Homo_sapiens /GRCh37.74	R883H	R	H	-1.43	9	Decrease
rs377603311	Homo_sapiens /GRCh37.74	R721H	R	H	-1.43	9	Decrease
rs377603311	Homo_sapiens /GRCh37.74	R707H	-	-	-	-	-
rs377603311	Homo_sapiens /GRCh37.74	R506H	R	H	-1.43	9	Decrease

Note: - indicate absence of prediction results

considered benign by Polyphen-2 while 26 snSNPs that did not showed any prediction results; both benign and non-prediction snSNPs they are excluded from this study.

### Meta-SNP

According to Meta-SNP prediction I showed the following results:-

PhD-SNP showed 69 snSNPs considered as disease in addition to other 9 nSNPs that were excluded due to they gave benign by Polyphen-2, 32 snSNPs were considered neutral in addition to other 6 nSNPs that were excluded due to they gave benign by Polyphen-2 while 26 snSNPs showed no predictions result, both benign and non-prediction snSNPs they are excluded from this study.

SIFT results showed 78 snSNPs as disease in addition to other 10 snSNPs that were excluded due to they predict benign by Polyphen-2, 22 snSNPs showed neutral in addition to other 5 snSNPs that where considered benign by Polyphen-2, 2 snSNPs showed NA and 26 snSNPs showed no results both benign and non-prediction snSNPs they are excluded from this study.

SNAP prediction illustrate 76 snSNPs as disease in addition to other 8snSNPs that excluded considered by Polyphen-2 due to benign predictions, 26 snSNPs they are neutral with 7snSNPs as benign by polyphen-2 and 26 snSNPs without any information.

Meta- SNP prediction showed 68 snSNPs as disease disease in addition to other 7 snSNPs that considered benign by polyphen-2 and exclude from this study; 34 snSNPs predicted as neutral disease in addition to other 8 snSNPs which was considered benign by – polyphen-2 and 26 snSNPs without any prediction information, those without prediction with those considered benign by polyphen-2 are excluded from this study too (Table 4).

### Discussion

Hemophilia is one of the hematologic important disease especially type A then followed by type B and C here in Sudan we showed hemophilia in a higher numbers of population may be due to habits of relative marriage beside cost of treatment was very expensive; in this study I used *in-silico* methods in translation topic to detect some SNP effects on already available untested database for hemophilia B; according to those tools that I was already used such as Proven, sift, polyphen-2, I mutant suite 3, SNPs & GO and Meta-SNP prediction, I found the previous results in addition to that there are some differences between these methods results specially when trying to confirm their results with another tools, which represented in the followings; In rs56309301→N243T it represented deleterious, tolerated, neutral, neutral according to sift, sift & proven, sift in meta-snp sequential, in rs111254723→(Y550C, Y888C, Y927C) represented deleterious, neutral, tolerated, disease; rs111254723→(Y751C) represented deleterious, neutral, tolerated, without sift from meta-snp prediction; rs143010673→(W137C) deleterious, deleterious,

damaging, neutral; rs143554211→(R695C) deleterious, neutral, damaging, without prediction; rs143554211→(R494C) deleterious, neutral, damaging, neutral; rs143554211→(R259C, R832C, R871C, R709C) deleterious, neutral, damaging, disease; rs143686298 →(P732T, P771T) deleterious, neutral, damaging, neutral; rs147901996→(N106S) deleterious, deleterious, damaging, neutral; rs148745528→(K99E) deleterious, deleterious, damaging, NA; rs148745528→(K253E) deleterious, deleterious, damaging, neutral; rs185306467→(I136N, I197N) deleterious, deleterious, damaging, neutral; rs188947672→(L706V, L728V) deleterious, neutral, damaging, disease; rs188947672→(L155V) tolerated, neutral, damaging, disease; rs189785572→( A501S, A386S) deleterious, neutral, damaging, disease/ without meta-snp prediction; rs193252599→(E168K, E604K) deleterious, neutral, tolerated/damaging, disease/ without meta-snp prediction; rs199892342→( V671A) deleterious, neutral, damaging, without meta-snp prediction; rs200172149→(T202A) deleterious, neutral, tolerated, neutral; rs200244068→(D106G, D167G) deleterious, deleterious, damaging, neutral; rs200395679→(A104T) deleterious, neutral, damaging, disease; rs200919195→(Y195F) deleterious, neutral, tolerated, neutral; rs368282144→( P299A, P453A, P338A) deleterious, deleterious, damaging, neutral/ neutral/without meta-snp prediction; rs368282144→(P514A, P475A) deleterious, deleterious, tolerated, disease; rs369226504→(T202R, T775R, T814R) deleterious, deleterious, damaging, disease; rs369226504→(T437R, T652R, T638R) deleterious, neutral, damaging, disease/ disease /without meta-snp prediction; rs369814333→(N81I, N517I) deleterious, deleterious/neutral, tolerated, neutral/ without meta-snp prediction; rs369909997→(N228D )deleterious, neutral, tolerated, neutral; rs370084230→(R10Q) deleterious, deleterious, damaging, neutral; rs370668897→(K51T )deleterious, deleterious, damaging, neutral; rs372752293→(T49R) deleterious, deleterious, damaging, neutral; rs374222815 →(V505M, V843M, V882M, V720M, V706M) deleterious, neutral, damaging, disease/ disease/ disease/ disease/ without meta-snp prediction ; rs374879205→(P512A, P713A, P850A, P889A, P727A) deleterious, deleterious, damaging, neutral /without meta-snp prediction /disease/disease/disease; rs375020232→(R200L) deleterious, deleterious, damaging, disease; rs375164425→(I57V, I96V) deleterious, neutral, tolerated, NA/ without meta-snp prediction; rs375553851→(N703H, N152H, N588H, N725H, N764H) deleterious, neutral/ deleterious/neutral/ neutral/ neutral, damaging, disease; rs375640863→(D435G, D281G, D320G, D457G) deleterious, deleterious, damaging, neutral/disease/ without meta-snp prediction/ disease; rs377266054→(E511V, E626V) deleterious, neutral, damaging, without meta-snp prediction /disease; rs377603311→(R844H, R883H, R721H, R707H, R506H) deleterious, deleterious /deleterious /neutral/deleterious /deleterious, damaging, disease/ disease/ disease/ without meta-snp prediction /disease; these represented sequential predictions for sift, sift & proven, sift in meta-snp ordinary.

PhD-SNP prediction for both SNPs & GO and Meta-snp tools showed similar prediction, in addition to some similarity or very tiny differences in PhD-SNP probability score.

Table 4: Illustrate SNPs & GO, Meta-SNP prediction results.

SNP	PhD-SNP prediction	PhD-SNP IR	PhD-SNP probability	SNPS & GO prediction	SNPS & GO IR	SNPS & GO probability	Meta- SNP prediction	Meta- SNP Probability	Meta-SNP IR
rs1145232	Disease	4	0.69	Neutral	0	0.496	Disease	0.697	4
rs1145232									
rs1145232	Disease	6	0.79	Disease	2	0.578	Disease	0.733	5
rs1145232	Disease	6	0.782	Disease	4	0.703	Disease	0.75	5
rs1145232	Disease	6	0.783	Disease	4	0.703	Disease	0.764	5
rs5742973	Disease	4	0.718	Neutral	0	0.484	Disease	0.698	4
rs56309301	Neutral	6	0.2	Neutral	9	0.063	Neutral	0.163	7
rs61756360	Disease	7	0.831	Disease	5	0.733	Disease	0.703	4
rs111254723	Neutral	5	0.272	Neutral	8	0.083	Neutral	0.174	7
rs111254723									
rs111254723	Neutral	2	0.389	Neutral	7	0.156	Neutral	0.234	5
rs111254723	Neutral	1	0.454	Neutral	6	0.183	Neutral	0.304	4
rs142159998	Disease	5	0.729	Disease	5	0.75	Disease	0.683	4
rs142159998	Disease	5	0.728	Disease	5	0.749	Disease	0.686	4
rs142159998	Disease	5	0.728	Disease	5	0.749	Disease	0.686	4
rs143010673									
rs143010673	Neutral	2	0.386	Neutral	2	0.417	Disease	0.537	1
rs143010673	Neutral	2	0.386	Neutral	1	0.441	Disease	0.703	4
rs143554211									
rs143554211	Disease	3	0.638	Neutral	2	0.379	Neutral	0.457	1
rs143554211	Neutral	0	0.484	Neutral	4	0.281	Neutral	0.448	1
rs143554211	Disease	6	0.81	Disease	2	0.625	Disease	0.649	3
rs143554211	Disease	6	0.812	Disease	3	0.626	Disease	0.645	3
rs143554211	Disease	6	0.814	Disease	3	0.628	Disease	0.651	3
rs143686298	Neutral	1	0.457	Neutral	7	0.155	Neutral	0.259	5
rs143686298	Neutral	1	0.472	Neutral	7	0.162	Neutral	0.322	4
rs145103030	Disease	6	0.778	Neutral	1	0.438	Disease	0.648	3
rs145103030	Disease	7	0.841	Disease	3	0.661	Disease	0.7	4
rs145103030									
rs145103030	Disease	7	0.842	Disease	3	0.672	Disease	0.701	4
rs145103030	Disease	7	0.843	Disease	4	0.688	Disease	0.7	4
rs145521752	Disease	5	0.757	Disease	4	0.687	Disease	0.603	2



rs145521752	Disease	5	0.76	Disease	4	0.687	Disease	0.643	3
rs145521752	Disease	5	0.761	Disease	4	0.688	Disease	0.65	3
rs145521752									
rs145521752	Disease	3	0.673	Disease	1	0.53	Disease	0.625	3
rs145521752	Disease	4	0.688	Disease	1	0.547	Disease	0.628	3
rs147901996									
rs147901996	Neutral 5 0.253	5	0.253	Neutral	8	0.088	Neutral	0.307	4
rs147901996	Neutral	7	0.158	Neutral	9	0.06	Neutral	0.244	5
rs148745528	Disease 2 0.612	2	0.612	Disease	5	0.765	Disease	0.681	4
rs148745528									
rs148745528	Disease	5	0.729	Disease	6	0.811	Disease	0.824	6
rs148745528	Disease	6	0.803	Disease	7	0.861	Disease	0.861	7
rs148745528	Disease	6	0.811	Disease	7	0.859	Disease	0.872	7
rs185306467									
rs185306467	Disease	4	0.693	Disease	2	0.619	Disease	0.576	2
rs185306467	Neutral	1	0.469	Neutral	1	0.441	Disease	0.619	2
rs188947672	Neutral	6	0.194	Neutral	8	0.075	Neutral	0.221	6
rs188947672	Neutral	1	0.445	Neutral	6	0.214	Neutral	0.259	5
rs188947672									
rs188947672	Neutral	7	0.148	Neutral	9	0.056	Neutral	0.146	7
rs189785572	Disease	7	0.835	Disease	2	0.615	Disease	0.683	4
rs189785572									
rs193252599	Neutral	0	0.478	Neutral	4	0.302	Neutral	0.4	2
rs193252599									
rs199892342									
rs200172149	Neutral	1	0.433	Neutral	6	0.178	Neutral	0.237	5
rs200244068	Neutral	5	0.255	Neutral	8	0.11	Neutral	0.389	2
rs200244068	Neutral	2	0.4	Neutral	6	0.221	Disease	0.513	0
rs200395679	Disease	3	0.638	Disease	1	0.534	Neutral	0.462	1
rs200919195	Neutral	6	0.181	Neutral	9	0.073	Neutral	0.088	8
rs201944922	Disease	0	0.503	Neutral	4	0.284	Disease	0.639	3
rs368282144	Neutral	4	0.32	Neutral	8	0.081	Neutral	0.243	5
rs368282144									
rs368282144	Neutral	1	0.453	Neutral	8	0.109	Neutral	0.314	4

rs368282144	Disease	1	0.551	Neutral	6	0.208	Disease	0.617	2
rs368282144	Disease	1	0.551	Neutral	6	0.208	Disease	0.617	2
rs369226504	Disease	5	0.743	Disease	1	0.538	Disease	0.634	3
rs369226504	Disease 4 0.714	4	0.714	Disease	0	0.524	Disease	0.609	2
rs369226504	Disease	7	0.872	Disease	5	0.73	Disease	0.694	4
rs369226504									
rs369226504	Disease	7	0.871	Disease	4	0.724	Disease	0.693	4
rs369226504	Disease	7	0.868	Disease	4	0.724	Disease	0.681	4
rs369814333	Neutral	3	0.369	Neutral	4	0.282	Neutral	0.227	5
rs369814333									
rs369909997	Neutral	6	0.218	Neutral	9	0.032	Neutral	0.228	5
rs370084230	Neutral	2	0.379	Neutral	8	0.116	Neutral	0.251	5
rs370300640	Disease	7	0.866	Disease	6	0.819	Disease	0.756	5
rs370578519	Disease	4	0.719	Neutral	6	0.206	Disease	0.587	2
rs370578519									
rs370578519	Disease	5	0.728	Neutral	6	0.219	Disease	0.586	2
rs370578519	Neutral	1	0.462	Neutral	8	0.084	Neutral	0.292	4
rs370668897	Neutral	2	0.385	Neutral	7	0.145	Neutral	0.154	7
rs371745827	Disease	4	0.687	Disease	3	0.656	Disease	0.74	5
rs371745827	Disease	6	0.819	Disease	6	0.792	Disease	0.77	5
rs371745827									
rs371745827	Disease	6	0.819	Disease	6	0.792	Disease	0.77	5
rs371745827	Disease	6	0.819	Disease	6	0.792	Disease	0.766	5
rs371745827	Disease	3	0.671	Disease	3	0.647	Disease	0.68	4
rs371999153	Disease	8	0.898	Disease	8	0.876	Disease	0.868	7
rs372752293	Disease	7	0.852	Disease	8	0.885	Disease	0.858	7
rs372752293	Disease	8	0.882	Disease	8	0.89	Disease	0.791	6
rs374222815	Disease	2	0.624	Disease	0	0.524	Neutral	0.48	0
rs374222815									
rs374222815	Disease	3	0.654	Disease	1	0.544	Neutral	0.471	1
rs374222815	Disease	3	0.654	Disease	1	0.544	Neutral	0.479	0
rs374222815	Disease	3	0.653	Disease	1	0.539	Neutral	0.483	0
rs374879205	Neutral	2	0.378	Neutral	7	0.142	Neutral	0.215	6
rs374879205									

rs374879205	Disease	1	0.558	Neutral	5	0.274	Disease	0.633	3
rs374879205	Disease	1	0.569	Neutral	4	0.289	Disease	0.633	3
rs374879205	Disease	2	0.579	Neutral	4	0.304	Disease	0.633	3
rs375020232	Disease	6	0.791	Disease	4	0.701	Disease	0.676	4
rs375020232	Disease	7	0.869	Disease	6	0.821	Disease	0.732	5
rs375020232									
rs375020232	Disease	7	0.869	Disease	6	0.82	Disease	0.734	5
rs375020232	Disease	7	0.868	Disease	6	0.82	Disease	0.707	4
rs375020232	Disease	6	0.778	Disease	4	0.692	Disease	0.71	4
rs375164425	Neutral	1	0.453	Neutral 0.268	5	0.268	Neutral	0.362	3
rs375164425									
rs375553851	Disease	1	0.528	Neutral 0.268	5	0.25	Disease	0.582	2
rs375553851	Neutral	2	0.392	Neutral	7	0.17	Neutral	0.24	5
rs375553851									
rs375553851	Disease	3	0.634	Neutral	1	0.436	Disease	0.607	2
rs375553851	Disease	3	0.641	Neutral	1	0.442	Disease	0.612	2
rs375640863	Disease	3	0.644	Neutral	4	0.295	Disease	0.566	1
rs375640863	Neutral	0	0.494	Neutral	6	0.218	Disease	0.566	1
rs375640863									
rs375640863	Disease	5	0.733	Neutral	0	0.498	Disease	0.634	3
rs377024581	Disease	8	0.921	Disease	6	0.797	Disease	0.637	3
rs377266054									
rs377266054	Neutral	2	0.405	Neutral	6	0.197	Neutral	0.262	5
rs377603311	Disease	4	0.694	Disease	4	0.708	Disease	0.606	2
rs377603311	Disease	4	0.694	Disease	4	0.708	Disease	0.606	2
rs377603311	Disease	4	0.693	Disease	4	0.709	Disease	0.577	2
rs377603311									
rs377603311	Disease	3	0.638	Disease	2	0.58	Neutral	0.444	1

Note: Empty row explained absence of prediction.

SNPS & GO prediction, SNAP and Meta- SNP prediction were different in:

rs1145232→(G286R) Neutral, Disease, Disease;  
 rs5742973→(E27Q) Neutral, Disease, Disease; rs56309301→(N243T)  
 Neutral, Disease, Disease; rs111254723→(Y888C, Y927C) Neutral,  
 Disease, Neutral; rs143010673→(W137C, W198C) Neutral,  
 Neutral, Disease/ Neutral, Disease, Disease; rs143554211→(R259C)  
 Neutral, Disease, Neutral; rs145103030→(R542C) Neutral,  
 Disease, Disease; rs147901996→(N260S) Neutral, Disease,

Neutral; rs185306467→(I136N, I197N) Disease, Neutral, Disease/  
 Neutral, Neutral, Disease; rs188947672→(L706V, L155V )  
 Neutral, Disease, Neutral; rs193252599→(E168K) Neutral,  
 Disease, Neutral; rs200172149→(T202A) Neutral, Disease,  
 Neutral; rs200244068→(D167G) Neutral, Neutral, Disease;  
 rs200395679→(A104T ) Disease, Neutral, Neutral; →(L4S )  
 Neutral, Disease, Disease; rs368282144→(P514A, P475A)  
 Neutral, Disease, Disease; rs370084230→(R10Q) Neutral,  
 Disease, Neutral; rs370578519→(P661L, P700L, P639L)

Neutral, Disease, Disease/ Neutral, Disease, Disease/ Neutral, Disease, Neutral; rs372752293→(T49R) Disease, Neutral, Disease; rs374222815→(V505M) Disease, Neutral, Neutral; rs374222815→(V843M,V882M,V720M) Disease, Neutral, Neutral; rs374879205→(P850A, P889A, P727A) Neutral, Disease, Disease; rs375553851→(N703H, N725H, N764H, N152H) Neutral, Disease, Disease/ Neutral, Disease, Disease/ Neutral, Disease, Disease/Neutral, Disease, Neutral; rs375640863→(D435G, D281G, D457G) Neutral, Disease, Disease; rs377266054→(E626V) Neutral, Disease, Neutral; rs377603311→(R506H) Disease, Disease, Neutral; those were not mention they are similar among the three prediction tools SNPS & GO prediction, SNAP and Meta- SNP prediction sequential.

In rs371999153→W49C was different from others SNPs because it's responsible for ORMDL1 gene or (ORF Names: HSPC202) that located in the same chromosome position 2 (2:189782449) (<https://www.ncbi.nlm.nih.gov/snp/?term=rs371999153>) similar to PMS1 gene, their protein called ORM1-like protein 1 or Adoplin-1; responsible for negative regulator of sphingolipid synthesis (<http://www.uniprot.org/uniprot/Q9P0S3>), ([https://www.ncbi.nlm.nih.gov/projects/SNP/snp\\_ref.cgi?rs=371999153](https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=371999153)), for Biological process is responsible for: (1) cellular sphingolipid homeostasis Source (2) ceramide metabolic process Source (3) negative regulation of ceramide biosynthetic process; they are widely expressed in adult and fetal heart, brain, lung, liver, skeletal muscle and kidney with expression in adult pancreas and placenta and in fetal spleen abdomen thymus while they expressed at intermediate level in pancreas, placenta and brain but low in skeletal muscle and lung, in addition they were found in subcellular location such as ERM (endoplasmic reticulum membrane) and multi-pass membrane protein.

The output of this study was explained and confirmed the damaging effect of those selected hemophilia B Snp.

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